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Mail Stop Appeal Brief Patents

In re application of: Toshiaki [illegible]GAWA et al.

Attorney Docket No. P21620

Application No. : 09/926,358

Group Art Unit : 1615

Filed : January 7, 2002

Examiner : Kishore

For : LIPOSOME BONDED WITH ANTIBODY AND POLYALKYLENE GLYCOL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Appeal Brief-Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

Transmitted herewith is an **Appellant's Reply Brief under 37 C.F.R. § 41.41 in Response to Examiner's Answer** in the above-captioned application.

____ Small Entity Status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a previously filed statement.

____ Exhibit 1.

____ A Request for Extension of Time.

_X_ No additional fee is required.

The fee has been calculated as shown below:

Claims After Amendment	No. Claims Previously Paid For	Present Extra	Small Entity		Other Than A Small Entity	
			Rate	Fee	Rate	Fee
Total Claims: 14	*20	0	x25=	$	x 50=	$ 0.00
Indep. Claims: 1	**3	0	x100=	$	x200=	$ 0.00
Multiple Dependent Claims Presented			+180=	$	+360=	$ 0.00
Extension Fees for ____ Month(s)				$		$ 0.00
Appeal Brief Filing Fee						$ 0.00
* If less than 20, write 20 ** If less than 3, write 3			Total:	$	Total:	$ 0.00

____ Please charge my Deposit Account No. 19-0089 in the amount of $_____.

N/A A check in the amount of $____ to cover the filing fee is included.

_X_ The U.S. Patent and Trademark Office is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 19-0089.

_X_ Any additional filing fees required under 37 C.F.R. 1.16.

_X_ Any patent application processing fees under 37 C.F.R. 1.17, including any required extension of time fees in any concurrent or future reply requiring a petition for extension of time for its timely submission (37 C.F.R. 1.136(a)(3)).

Bruce H. Bernstein
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Toshiaki TAGAWA et al.

Appl No : 09/926,358

Filed : January 7, 2002

For : LIPOSOME BONDED WITH ANTIBODY AND POLYALKYLENE GLYCOL

Group Art Unit: 1615

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APPELLANTS' REPLY BRIEF UNDER 37 C.F.R. 41.41 IN RESPONSE TO EXAMINER'S ANSWER

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Appeal Brief – Patent
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

Further to an Examiner's Answer mailed August 9, 2006, the following is Appellants' response.

Appellants submit that the Examiner's Answer does not address the deficiencies of the rejections set forth in the Final Rejection, and does not fully respond to Appellants' arguments set forth in Appellants' Appeal Brief filed May 15, 2006 so that the final rejections remain without sufficient basis.

Appellants' arguments for patentability are set forth in their Appeal Brief. Therefore, for the sake of brevity, this Reply Brief does not repeat each of the arguments set forth in the Appeal Brief, but incorporates these arguments herein as if set forth in their entirety. This Reply Brief addresses arguments set forth by the Examiner in the

Examiner's Answer, and points out deficiencies in these arguments while emphasizing arguments set forth by Appellants.

Anticipation Rejection Based Upon Tagawa '221, U.S. Patent No. 5,264,221

Appellants' Appeal Brief presents arguments that Tagawa '221 does not disclose the subject matter recited in Appellants' claims with "sufficient specificity" to constitute an anticipation of the claims. As part of these arguments, it is pointed out in the Appeal Brief, at page 15, last full paragraph, with respect to the examples of Tagawa '221 that, "The amounts of bound antibody and the bound PEG in the liposome disclosed in Tagawa '221 are 5 mg/100 mg lipids and 47 mol% per 1 mol of maleimidated lipids." The rejection does not provide appropriate support as to how such disclosure anticipates Appellants' claimed subject matter which includes, amongst other features, "an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome".

Regarding Appellants' recited amount of antibody being 1.2 to 2 mg per 100 mg of total lipids, the Examiner's Answer contends that Tagawa '221 broadly discloses an antibody range of 0.3 to 60 mg, and Tagawa's example uses 5 mg. From this, the Examiner's Answer contends that 5 mg is closer to the lower limit of 0.3 mg than the upper limit of 60 mg, and "not far away from 1.2 to 2 mg in claim 16". The Examiner's Answer concludes from this reasoning that, "although Tagawa 221 teaches a broader

range, the example is closer to the claimed range." However, the Examiner's Answer does not indicate what is meant by "the example is closer to the claimed range" or whether this asserted closeness constitutes "sufficient specificity" to constitute anticipation. Appellants submit that this is not a sufficient disclosure to constitute anticipation of Appellants' recited subject matter.

Further, regarding the recitation of the amount of the bonded compound being 15 to 30 mole% based on one mole of the maleimidated lipid, the Examiner's Answer disagrees with Appellants' arguments and points to column 4, lines 64-66 of Tagawa '221. The Examiner's Answer contends that polyalkylene glycol is added in Tagawa '221 in an amount of at least twice in equivalent to the antibody. The Examiner's Answer contends that the antibody in Tagawa '221 is added in an amount of 0.1 % to 20 mole %, and that at least twice the amount would be 0.2 % to 40 %, and that this range encompasses Appellants' recited 15 to 30 mole %.

In contrast to the arguments presented in the Examiner's Answer and as noted in Appellants' Appeal Brief, the amount of the bound PEG in the examples of Tagawa '221 is 47 mole% per one mole of maleimidated lipids, which is not within Appellants' claimed range. The at least twice in equivalent disclosed in Tagawa '221 appears to be with respect to the remaining maleimide groups, and not with respect to the antibody, as contended in the Examiner's Answer.

Thus, Tagawa '221 does not disclose, and therefore does not anticipate, Appellants' claimed subject matter, which includes amongst other features, "amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid,

and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome".

Regarding Appellants' showing of unexpected results, the Examiner's Answer refers to certain of Appellants' arguments, and contends that, "This statement clearly indicates that irrespective of whether the antibody amount is outside the claimed range or inside the claimed range, the results are significant meaning that even 221 results are unexpected."

Appellants' appreciate that the Examiner's Answer recognizes that Appellants' claimed subject matter provides unexpected results. However, the Examiner's Answer does not completely address the unexpected results shown by Appellants as compared to Tagawa '221.

As pointed out in Appellants' Appeal Brief, the unexpected advantages of using a smaller amount of bound antibody according to Appellants' invention is also apparent from a review of Appellants' Example 4 in their originally filed application. **As explained in Example 4, a smaller amount of bound antibody gives a higher therapeutic effect, and this result is unexpected by one of ordinary skill in the art in view of Tagawa '221 which discloses the use of a larger amount of bound antibody than the presently claimed liposome, medicament composition and method.** Therefore, Appellants' originally filed specification, including Example 4, provides evidence of the unexpectedly advantageous results associated with Appellants' invention.

In particular, in Appellants' Example 4, liposomes 2-7 containing varying amounts of GAH antibody (0.5, 1.2, 2.0, 4.5, 5.3 and 11.4 mg) bonded to 100 mg of the total lipids of the liposome encapsulating doxorubicin (DXR, also referred to as adriamycin) were prepared according to the method of Example 1. Also, liposomes 1 bonded with no antibody were prepared. For convenience Table 3 from Appellants' specification including the content of the liposomes in the specification was reproduced in the Appeal Brief including modification to include conversion to amount of bound PEG (per 1 mol of maleimidated lipids), and is again reproduced below.

Liposome disclosed in Example 4	Amount of bonded antibodies (mg/100 mg lipids)	Amount of included DXR (mg/100 mg lipids)	Amount of bonded PEG (mg/100 mg lipids)	Amount of bound PEG (per 1 mol of maleimidated lipids
1	0	9.5	8.2	28 mol%
2	0.5	9.1	8.2	28 mol%
3	1.2	9.5	8.1	28 mol%
4	2.0	8.9	5.3	18 mol%
5	4.5	9.6	6.2	21 mol%
6	5.3	9.7	6.4	22 mol%
7	11.4	10.0	3.2	11 mol%
Tagawa '221	Fab' antibody 5 mg			47 mol%

Example 4 further notes that retention of each liposome in blood was equivalent within the range of the amount of PEG bonded (> 4.4 mg/100 mg lipids), and Example 4 therefore indicates that the experimental results shown in the examples depended on the bonded amount of antibodies.

In Example 4, stomach cancer cell strain MKN45 was subcutaneously transplanted at two sites on nude mice. For the "efficacy test", administrations of liposomes with different amounts of bonded antibodies were started when the tumor reached to a size large enough to measure its long and short diameters. The dose of the liposomes was 5.0 mg/kg (as the amount of DXR) per administration, and a DXR-administered group (5.0 mg/kg) was provided as a positive control, and physiological saline was administered to the control group.

Significant inhibitory effects against tumor proliferation were found in all of the treated groups compared with the control group. A review of Fig. 3 in Appellants' application, when comparison is made to the DXR-administered group, reveals significant inhibitory effects against tumor proliferation in the samples with the amounts of bonded antibodies within the range of 0.5 to 5.3 mg/100 mg of total lipids. The inhibitory activity against tumor proliferation was observed with a peak in the vicinity of 2 mg/100 mg of total lipids as the amount of bonded antibodies.

In the "pharmacokinetic test", liposomes 4 to 7 with different amounts of bonded antibodies (2.0, 4.5, 5.3 and 11.4 mg/100 mg of total lipids) were intravenously administered to mice (each group consisted of 2 or 3 mice, 1.0 mg/kg as the amount of DXR amount). Four hours after the administration, blood plasma was collected from each animal. The amount of DXR in plasma was measured by the fluorescence measurement method in the same manner as in Example 2. The amounts of DXR in plasma in the respective samples after the administration were compared to find correlation between the amount of bonded antibodies and the retention in blood of the liposomes

encapsulating DXR and bonded with antibodies. In the pharmacokinetic test, correlation between the DXR amount in plasma after administration of each sample and the amount of bonded antibodies of each sample was obtained for samples having the amount of the bonded antibodies of 2 mg/100 mg of lipids or more, as can be seen from a review of Fig.4 in Appellants' application. As a result, it was found that, when the amount of the bonded antibodies exceeded 2 mg/100 mg of the lipids, the retention in blood decreased depending on the increasing amount of the bonded antibodies.

The Examiner's Answer does not respond to this unexpected showing in Appellants' originally filed application of a decrease in retention in blood depending on the increasing amount of the bonded antibodies when the amount of bonded antibodies exceeded 2 mg/100 mg of the lipids.

For at least these reasons in addition to the reasons set forth in Appellants' Appeal Brief, the anticipation rejection based upon Tagawa '221 is without appropriate basis, and should be reversed.

Obviousness Rejection Based Upon Tagawa '221, U.S. Patent No. 5,264,221

Appellants point out in the Appeal Brief that the obviousness rejection based upon Tagawa '221 is in error, and the decision of the Examiner to finally reject the claims should be reversed.

The Examiner's Answer does not overcome the deficiencies of the Examiner's final rejection and, in fact, adds to the unclear basis for the rejection set forth in the final rejection.

In the middle of page 7 of the Examiner's Answer, it is contended that, "Furthermore, in Example 2 on col. 7, Tagawa uses 5 mg of Fb' per hundred mg of lipid and this amount is instantly claimed 5 mg per 100 mg lipid." In contrast to this assertion, , Appellants' are not claiming 5 mg per 100 mg lipid as asserted, but "an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome."

Moreover, once again, the Examiner's Answer that does not completely address the showings of unexpected results shown in Appellants' originally filed application.

For at least these reasons in addition to the reasons set forth in Appellants' Appeal Brief, the obviousness rejection based upon Tagawa '221 is without appropriate basis, and should be reversed.

Obviousness Rejection Based Upon Kirpotin et al. (Kirpotin), Biochemistry, 1997, In Combination With Tagawa '221, U.S. Patent No. 5,264,221

Appellants point out in the Appeal Brief that the obviousness rejection based upon the combination of Kirpotin and Tagawa '221 is in error, and the decision of the Examiner to finally reject the claims should be reversed.

The Examiner's Answer does not overcome the deficiencies of the Examiner's final rejection, especially when the Examiner's Answer does not completely address the showings of unexpected results shown in Appellants' originally filed application. For the sake of brevity, Appellants' are not repeating these arguments, but incorporate the remarks set forth in the Appeal Brief and the remarks included above.

For at least these reasons in addition to the reasons set forth in Appellants' Appeal Brief, the obviousness rejection based upon Kirpotin in combination with Tagawa '221 is without appropriate basis, and should be reversed.

Obviousness Rejection Based Upon Hosokawa '153, U.S. Patent No. 6,787,153, or Hosokawa '869, U.S. Patent No. 6,139,869.

Appellants point out in the Appeal Brief that the obviousness rejections based upon either of Hosokawa '153 or Hosokawa '869 are in error, and the decision of the Examiner to finally reject the claims should be reversed.

The Examiner's Answer does not overcome the deficiencies of the Examiner's final rejection, especially when, as noted above, the Examiner's Answer does not completely address the showings of unexpected results shown in Appellants' originally filed application. For the sake of brevity, Appellants' are not repeating these arguments, but incorporate the remarks set forth in the Appeal Brief and the remarks included above.

In order that the record is clear, Appellants note that the quote at page 43 of the Appeal Brief with respect to this rejection includes typographical errors, and this quote should appear as follows: "Applicant admits on page 26 of the response that HosoKawa 153 and 869 disclose the same amount of antibody and the same amount of PEG as Tagawa 221 and therefore, the examiner's response is similar to that for their arguments regarding Tagawa, 221." Moreover, Appellants note that the correct spelling is

Hosokawa and not Hosakawa as originally indicated in the Examiner's February 8, 2005 Office Action and included in Appellants' Appeal Brief.

For at least these reasons in addition to the reasons set forth in Appellants' Appeal Brief, the obviousness rejection based upon Hosokawa '153 and Hosokawa '869 is without appropriate basis, and should be reversed.

Obviousness-Type Double Patenting Rejections Based Upon Hosokawa '153, U.S. Patent No. 6,787,153, or Hosokawa '869, U.S. Patent No. 6,139,869.

Appellants point out in the Appeal Brief that the obviousness-type double patenting rejections based upon either of Hosokawa '153 or Hosokawa '869 are in error, and the decision of the Examiner to finally reject the claims should be reversed.

The Examiner's Answer does not overcome the deficiencies of the Examiner's final rejection, especially when, as noted above, the Examiner's Answer does not completely address the showings of unexpected results shown in Appellants' originally filed application. For the sake of brevity, Appellants' are not repeating these arguments, but incorporate the remarks set forth in the Appeal Brief and the remarks included above. However, Appellants stress that the rejection does not address motivation to arrive at Appellants' claimed subject matter from the claims of either of Hosokawa "153 or Hosokawa '869.

For at least these reasons in addition to the reasons set forth in Appellants' Appeal Brief, the obviousness rejection based upon Hosokawa '153 and Hosokawa '869 is without appropriate basis, and should be reversed.

For the reasons expressed in Appellants' Appeal Brief, and as further presented herein, Appellants respectfully request that the grounds of rejection advanced by the Examiner be reversed and that the Examiner's final rejection be reversed.

Although a fee is not believed to be due with this Reply Brief, Appellants authorize the charging of any necessary fee for maintaining the pendency of this application, including any fee required for entry and/or consideration of this Reply Brief, to Deposit Account No. 19-0089.

Appellants respectfully request that the Board reverse the decision of the Examiner to reject claims 16-23, 32-34 and 37.

If the Examiner has any questions or wishes to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
Toshiaki Tagawa et al.

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October 10, 2006
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